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Review Article

REVIEW ON NOVEL OSMOTIC DRUG DELIVERY SYSTEM

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ABSTRACT

Novel drug delivery systems (NDDS) are the key area of pharmaceutical research and Development. The reason is relatively low development cost and time required for introducing a NDDS as compared to new chemical entity. Many conventional drug delivery systems have been designed to modulate the release a drug over an extended period of a time. Various designs are available to control or modulate the drug release from a dosage forms. Majority of oral CR dosage forms fall in the category of matrix, reservoir or osmotic systems. Osmotically controlled drug delivery systems (OCDDS) is one of the most promising drug delivery technology that use osmotic pressure as a driving force for controlled delivery of active agents. Drug release from OCDDS is independent of pH and hydrodynamic conditions of the body because of the semipermeable nature of the Rate controlling membrane and the design of deliver orifice used in osmotic systems, so a high degree of In vitro/In vivo correlation is achieved. Osmotic drug delivery systems release the drug with the zero order kinetics which does not depend on the initial concentration and the physiological factors of GIT. This review brings out new technologies, fabrication and recent clinical research in osmotic drug delivery.

Keywords: Osmotic, Matrix, Reservoir, Fabrication

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INTRODUCTION

Novel drug delivery systems (NDDS) are the key area of pharmaceutical research and Development. The reason is relatively low development cost and time required for introducing a NDDS as compared to new chemical entity. Many conventional drug delivery systems have been designed to modulate the release a drug over an extended period of a time[1]. Various designs are available to control or modulate the drug release from a dosage forms. Majority of oral CR dosage forms fall in the category of matrix, reservoir or osmotic systems. Conventional matrix or reservoir type formulations exhibits problem of bioavailability fluctuations due to gastric pH variations. Moreover, the release of drugs from these systems is affected by the hydrodynamic conditions of the body. The rate and extent of drug absorption from conventional formulations may vary greatly depending on the factors such as physico-chemical properties of the drug, presence of Excipients, physiological factors such as presence or absence of food, pH of the gastro-intestinal tract (GI) and so on [2]. However, drug release from oral controlled release dosage forms may be affected by pH, GI motility and presence of food in the GI tract[3]. Osmotically controlled drug delivery systems (OCDDS) is one of the most promising drug delivery technology that use osmotic pressure as a driving force for controlled delivery of active agents. Drug release from OCDDS is independent of pH and hydrodynamic conditions of the body because of the semi permeable nature of the Rate-controlling membrane and the design of deliver orifice used in osmotic systems, so a high degree of In vitro/In vivo correlation is achieved.[4, 5]

Osmosis can be defined as the net movement of water across a selectively permeable membrane driven by a difference in osmotic pressure across the membrane. It is

driven by a difference in solute concentrations across the membrane that allows passage of water, but rejects most solute molecules or ions. Osmotic pressure is the pressure which, if applied to the more concentrated solution, would prevent transport of water across the semi permeable membrane. Osmotic Pump Controlled Release Preparation is a novel drug delivery system with eternally drug delivery rate as characteristic and controlled with the osmotic pressure difference between inside and outside of the semipermeable membrane as drug delivery power [6].Recently, osmotic tablets have been developed in which the delivery orifice is formed by the incorporation of a leachable component in the coating. Once the tablet comes in contact with the aqueous environment, the water-soluble component dissolves, and an osmotic pumping system results. Subsequently, water diffuses into the core through the micro porous membrane, setting up an osmotic gradient and thereby controlling the release of drug. Osmosis can be defined as the spontaneous movement of a solvent from a solution of lower solute concentration to a solution of higher solute concentration through an ideal semipermeable membrane, which is permeable only to the solvent but impermeable to the solute. The pressure applied to the higher-concentration side to inhibit solvent flow is called the osmotic pressure.

Advantages of Osmotic Drug Delivery System[7, 8]

Apart from the general advantages of controlled drug delivery systems, osmotic pumps have

Certain unique advantages, as follows:

1. Delivery of drug from osmotic pumps can be designed to follow true zero-order kinetics.

2. Delivery may be delayed or pulsed, if desired.

3. Drug release from osmotic pumps is independent of the gastric pH and hydrodynamic

Conditions of the body.

4. Higher release rates are possible from osmotic systems than with conventional diffusion

Based drug delivery systems.

5. The delivery rate of drug(s) from these systems is highly predictable and programmable

by modulating the release control parameters.

6. A high degree of *In vitro/In vivo* correlation can be obtained from osmotic pumps.

7. Drug release from the osmotic systems is minimally affected by the presence of food.

Classification of Osmotic Pump Drug Delivery System [9]

Implantable	**Oral osmotic Pump**	**Specific types**
The Rose and Nelson Pump	Single chamber osmotic pump - 1.*Elementary osmotic pump*	Controlled porosity osmotic pump,
Higuchi Leeper Pump	**Multi chamber osmotic pump: 1.Push pull osmotic pump, 2.Osmotic pump with non-expanding second chamber**	**Osmotic bursting osmotic pump**
Higuchi Theuwes pump		Liquid OROS,
		Delayed Delivery osmotic system
		OROS-CT (colon targeting),
		sandwiched oral therapeutic system
Implantable Mini osmotic pump		Osmotic pump for insoluble drugs,
		Monolithic osmotic system and OSMAT

Key Milestones in OCDDS development

Rose-Nelson Pump

About 75 years after discovery of the osmosis principle, it was first used in the design of drug delivery systems.(Rose and Nelson 415) Rose and Nelson, the Australian scientists, were initiators of osmotic drug delivery. In 1955, they developed an implantable pump, which consisted of three chambers: a drug chamber, a salt chamber contains excess solid salt, and a water chamber. The drug and water chambers are separated by rigid semipermeable membrane. The difference in osmotic pressure across the membrane moves water from the water chamber into the salt chamber. The volume of the salt chamber increases because of this water flow, which distends the latex diaphragm separating the salt and drug chambers, thereby pumping drug out of the device. The design and mechanism of this pump is comparable to modern push-pull osmotic pump. The major disadvantage of this pump was the water chamber, which must be charged before use of the pump [10]

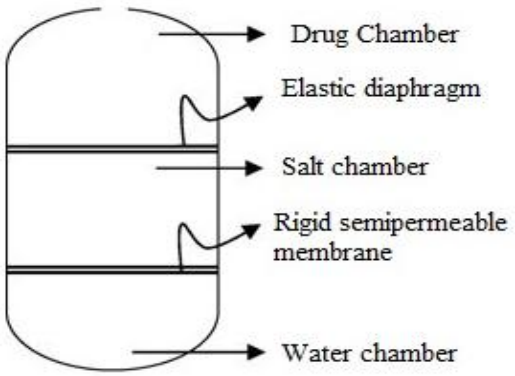

Figure 1: Rose-Nelson Pump

Several simplifications in Rose-Nelson pump were made by Alza Corporation in early 1970s. The Higuchi-Leeper pump is modified version of Rose-Nelson pump.

It has no water chamber, and the device is activated by water imbibed from the surrounding environment.

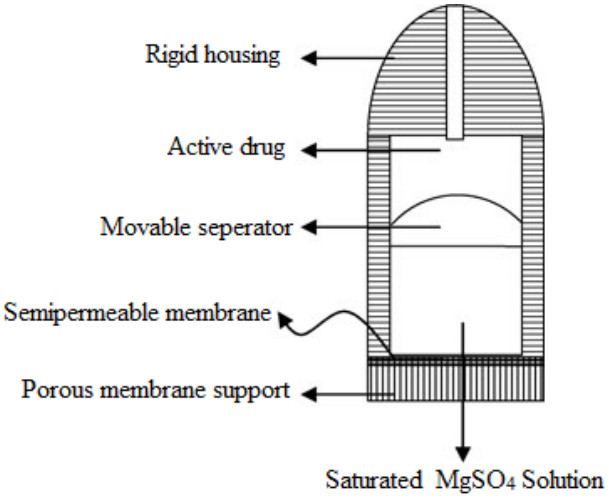

Figure 2: Higuchi-Leeper Pump

The pump is activated when it is swallowed or implanted in the body. This pump consists of a rigid housing, and the semi permeable membrane is supported on a perforated frame. It has a salt chamber containing a fluid solution with excess solid salt. Recent modification in Higuchi-Leeper pump accommodated pulsatile drug delivery. The pulsatile release was achieved by the production of a critical pressure at which the delivery orifice opens and releases the drug.(Higuchi and Leeper ; Higuchi and Leeper)[11]

Higuchi-Theeuwes Pump

In the early 1970s, Higuchi and Theeuwes developed another, even simpler variant of the Rose-Nelson pump. As with the Higuchi-Leeper pump, water to activate the osmotic action of the pump is obtained from the surrounding environment. In the Higuchi-Theeuwes device, however, the rigid housing is dispensed with and the membrane acts as the outer casing of the pump. This membrane is quite sturdy and is strong enough to withstand the pumping pressure developed inside the device. The device is loaded with the desired drug prior to use. When the device is placed in an aqueous environment, release of the drug follows a time course set by the salt used in the salt chamber and the permeability of the outer membrane casing. Most of the Higuchi-Theeuwes pumps use a dispersion of solid salt in a suitable carrier for the salt Chamber of the device.[12.13]

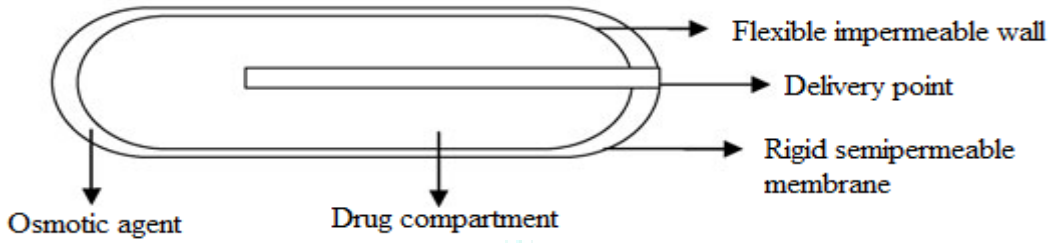

Figure 3: Theeuwes miniature osmotic pump

Implantable Mini osmotic pump

Implantable Mini osmotic pump shown in figure 3 it is composed of three concentric layers-the drug reservoir, the osmotic sleeves and the rate controlling semi permeable membrane. The additional component called flow moderator is inserted into the body of the osmotic. The inner most compartment of drug reservoir which is surrounded by an osmotic sleeve, a cylinder containing high concentration of osmotic agent. The osmotic sleeve is covered by a semi permeable membrane when the system is placed in aqueous environment water enters the sleeve through semi permeable membrane, compresses the flexible drug reservoir and displaces the drug solution through the flow moderator. These pumps are available with variety of delivery rates between 0.25 to 10ml per hour and delivery duration between one day and four weeks.[14 15]

Single chamber osmotic pump:

A. Elementary osmotic pump:-

Elementary osmotic pump was invented by Theeuwes in 1974 and it essentially contains an active agent having a suitable osmotic pressure, it is fabricated as a tablet coated with semi permeable membrane, usually cellulose acetate. 25 A small orifice is drilled through the membrane coating. (When this coated tablet is exposed to an aqueous environment, the osmotic pressure of the soluble drug inside the tablet draws water through the semi permeable coating and a saturated aqueous solution of drug is formed inside the device. The membrane is non-extensible and the increase in volume due to inhibition of water raises the hydrostatic pressure inside the tablet, eventually leading to flow of saturated solution of active agent out of the device through a small orifice. [16, 17]

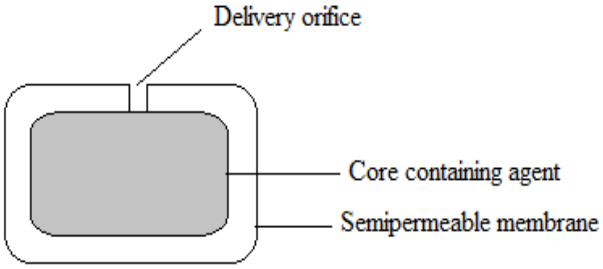

Figure 4: Elementary Osmotic Pump

B. Push–Pull Osmotic Pump (PPOP)

The two-layer push–pull osmotic tablet system appeared in 1980s. Push pull osmotic pump is a modified elementary osmotic pump through, which it is possible to deliver both poorly water-soluble and highly water soluble drugs at a constant rate. The push–pull osmotic tablet consists of two layers, one containing the drug and the other an osmotic agent and expandable agent. A semipermeable membrane that regulates water influx into both layers surrounds the system. While the push–pull osmotic tablet operates successfully in delivering water-insoluble drugs, it has a disadvantage that the complicated laser drilling technology should be employed to drill the orifice next to the drug compartment [18].

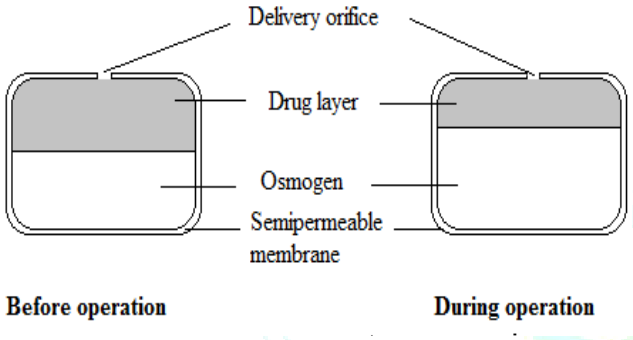

Figure 5: Push–Pull Osmotic Pump (PPOP)

C. Osmotic Pump with Non Expanding Second Chamber

The second category of multi-chamber devices comprises system containing a non-expanding second chamber. This group can be divided into two sub groups, depending on the function of second chamber. In one category of these devices, the second chamber is used to dilute the drug solution leaving the devices. This is useful because in some cases if the drug leaves the oral osmotic devices a saturated solution, irritation of GI tract is a risk. Example: The problem that leads to withdrawal of osmosin, the device consists of a normal drug containing porous tablet from which drug is released as a saturated solution. However before the drug can escape from the device it must pass through a second chamber. Water is also drawn osmotically into this chamber either because of osmotic pressure of drug solution or because the second chamber contain, water soluble diluents such as NaCl. This type of devices consist of two rigid chamber, the first chamber contains a biologically inert osmotic agent, such as sugar or a simple salt like sodium chloride, the second chamber contains the drug. In use water is drawn into both the chamber through the surrounding semi permeable membrane. The solution of osmotic agent formed in the first chamber then passes through the connecting hole to the drug chamber where it mixes with the drug solution before exiting through the micro porous membrane that form a part of wall surrounding the chamber. The device could be used to deliver relatively insoluble drugs.[19]

Specific types

Controlled Porosity Osmotic Pump

A controlled porosity osmotic pump-based drug delivery system Unlike the elementary osmotic pump (EOP) which consists of an osmotic core with the drug surrounded by a semipermeable membrane drilled with a delivery orifice, controlled porosity of the membrane is accomplished by the use of different channeling agents in the coating. The CPOP contains water soluble additives in coating membrane, which after coming in contact with water; dissolve resulting in an in-situ formation of a microporous membrane. Then the resulting membrane is substantially permeable to both water and dissolved solutes and the mechanism of drug release from these systems was found to be primarily osmotic, with simple diffusion playing a minor role [20, 21]. Drug delivery from asymmetric membrane capsule is principally controlled by the osmotic pressure of the core formation. In-situ formed delivery orifice in the asymmetric membrane in mainly responsible for the solubilization in the core for a drug with poor water solubility [22].

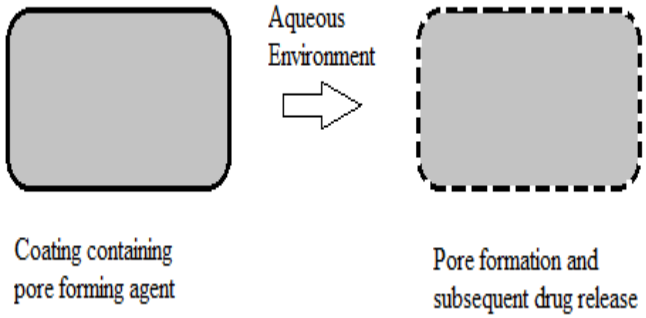

Figure 6: Controlled Porosity Osmotic Pump

Osmotic bursting osmotic pump

This system is similar to an EOP expect delivery orifice is absent and size may be smaller. When it is placed in an aqueous environment, water is imbibed and hydraulic pressure is built up inside until the wall rupture and the content are released to the environment. Varying the thickness as well as the area the semi permeable membrane can control release of drug. This system is useful to provide pulsated release . Liquid OROS: Liquid OROS are designed to deliver drugs as liquid formulations and combine the benefits of extended release with high bioavailability. They are of three types: a) L OROS hard cap b) L OROS soft cap c) delayed liquid bolus delivery system.[23]

Sandwiched Osmotic Tablets (SOTS)

In this a tablet core composed of polymeric push layer sandwiched between two drug layers with two delivery orifices. When placed in the aqueous environment the middle push layer containing the swelling agent swells and the drug is released from the two orifices situated on opposite sides of the tablet and thus SOTS can be suitable for drugs prone to cause local irritation of the gastric mucosa. [24]

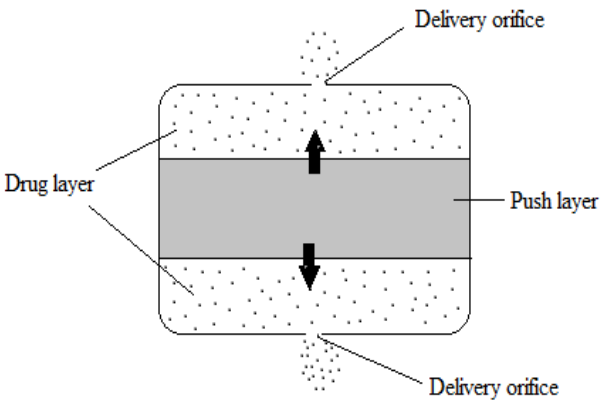

Figure 7: Sandwiched osmotic tablets

Osmotic pump for insoluble drugs: The device concerns an osmotic agent for dispensing beneficial active agent that has poor solubility in water. The core of the system comprises a beneficial amount of a substantially water-insoluble active agent, which is lipid soluble or lipid-wettable; a sufficient amount of water insoluble lipid carrier, which is liquid at the temperature of use to dissolve or suspend the drug and agent to ensure the release of the lipid carrier of the drug from the pump

Basic Component of Osmotic System

- Drug
- Osmotic agent
- Semipemiable membrane
- Wicking agent
- Pore forming

Drug

All drugs are not suitable for osmotic system as prolong action medication .Drugs those which has biological half-life more than 12 hr e.g.: Diazepam and drug which have very short half life i.e. less than 1 hr e.g. Penicillin G, furosemide are not suitable candidate for osmotic controlled release. Drug which have biological half-life in between 1 – 6 hrs and which is used for prolonged cure of diseases are ideal applicant for osmotic systems. [25]

Drug having following characteristics are suitable for formulation

1. It should have short half-life

2. Prolonged release of drug should be desired.

3. It should be potent in nature.

4. Solubility of drug should not be very high or very low. [26]

Osmotic agent

These are also known as osmogens or osmogents and are used to create osmotic pressure inside the system. When the solubility of drug is low then the drug will show zero order release but at a slow rate. To enhance the release rate osmotic agent is added in the formulation. Osmotic agent creates a very high osmotic pressure gradient inside the system and increases release rate of drug. [27]

Some of the commercially used osmotic agents

Sodium chloride, Fructose, sucrose, Potassium chloride, Xylitol, Sorbitol, citric acid, Dextrose, Manitole and Lactose.

Semi permeable Membrane

Since the membrane in osmotic systems is semi permeable in nature, any polymer that is permeable to water but impermeable to solute can be selected.13 Cellulose acetate is a commonly employed semi permeable polymer for the preparation of osmotic pumps. It is available in different acetyl content grades. Particularly, acetyl content of 32% and 38% are widely used. Acetyl content is described by the degree of substitution (DS), i.e. the average number of hydroxyl groups on the anhydroglucose unit of the polymer replaced by substituting group. Some of the polymers that can be used for above purpose include cellulose esters such as cellulose acetate, cellulose diacetate, cellulose triacetate, cellulose propionate, cellulose acetate butyrate, and cellulose ethers like ethyl cellulose. The Semi Permeable Membrane must meet some performance criteria.

- The material must possess sufficient wet strength (-105) and wet modulus so as to retain its dimensional integrity during the operational lifetime of the device.
- The membrane exhibit sufficient water permeability so as to retain water flux rate in the desired range. The water vapor transmission rates can be used to estimate water flux rates.
- The reflection coefficient and leakiness of the osmotic agent should approach the limiting value of unity. Unfortunately, polymer membranes that are more permeable to water are also, in general more permeable to the osmotic agent.
- The membrane should also be biocompatible.[28,29]

Wicking agent

The wicking agents are those agents which help to increase the contact surface area of the drug with the incoming aqueous fluid. The use of the wicking agent help to enhance the rate of drug released from the orifice of the drug. The examples are colloidal silicon dioxide, PVP & Sodium laryl sulphate. [30]

Pore Forming Agents

The pore-forming agents cause the formation of micro porous membrane. The micro porous wall may be formed in situ by a pore-former by its leaching during the operation of the system. The pore-formers can be inorganic or organic and solid or liquid in nature. For example, alkaline metal salts such as sodium chloride, sodium bromide, potassium chloride, potassium sulphate, potassium phosphate etc., alkaline earth metals such as calcium chloride and calcium nitrate, carbohydrates such as sucrose, glucose, fructose, mannose, lactose, sorbitol, and mannitol and, diols and polyols such as poly hydric alcohols, polyethylene

glycols and polyvinyl pyrrolidone can be used as pore forming agents.[31]

Coating solvents

The primary function of solvent system is to dissolved or dispersed the polymer and other additive and convey them to substrate surface. solvent used to prepare polymeric solution include inert inorganic and organic solvents that do not adversely harm the core ,wall and other material .the various types of solvents and their combinations are as follows: Methylene chloride, methanol, isopropyl alcohol, dichloromethane , ethyl acetate, acetone, carbon tetrachloride, cyclohexane, butyl alcohol, water etc and the mixture of solvents such as acetone-methanol(80:20), methylene chloride-methanol (79:21), acetone-ethanol(80:20), methylene chloride-methanol-water (75:22:3) [32]

Mechanism of drug release

Tablet has rigid water permeable jacket with one or more laser dried small holes. As the tablet passes through the body the osmotic pressure of the tablet pushes the active drug through the opening in the tablet. The basic equation which applies to osmotic systems is

$$dM/dt = dV/dt.c \quad \ldots\ldots(a)$$

Where,

dM /dt= mass release

dV/dt = volumetric pumping rate

c = concentration of drug But,

$$dV/dt = (A/h)Lp$$

(σ ΔΠ-Δp)

Where,

A= membrane area,

h= thickness of membrane,

Lp= mechanical permeability,

σ =reflection coefficient,

ΔΠ=osmotic pressure difference,

Δp = hydrostatic pressure difference

As the size of orifice delivery increases.

Δp decrease, so ΔΠ >> Δp and equation becomes

$$dV/dt = A/h\ Lp(\sigma \Delta\Pi)$$

When the osmotic pressure of the formulation is large compared to the osmotic pressure of the environment, p can be substituted for Dp.

$$dV/dt = A/h\ Lp$$

$$\sigma\Pi = A/hk\ \Pi$$

(k = Lpσ = membrane permeability), Now, equation (a) can be given as

dM / dt = (A / h) k Π c = (A / h) k Π S (S = solubility of drug, c taken as S)

CONCLUSION

In osmotic delivery systems, osmotic pressure provides the driving force for drug release. Increasing pressure inside the dosage form from water incursion causes the drug to release from the system. The major advantages include precise control of zero-order or other patterned release over an extended time period consistent release rates can be achieved irrespective of the environmental factors at the delivery site. However, a complex manufacturing process and higher cost compared with conventional dosage. Forms limit their use. Although not all drugs available for treating different diseases require such precise release rates, once-daily formulations based on osmotic principles are playing an increasingly important role in improving patient compliance. Therefore, most of the currently marketed products are based on drugs used in long-term therapies for diabetes, hypertension, attention-deficit disorder, and other chronic disease states. Besides oral osmotic delivery systems, implants that work on osmotic principles are promising for delivery of a wide variety of molecules with a precise rate over a long period of time. Further, with the discovery of newer and potent drugs by the biotechnology industry, the need to deliver such compounds at a precise rate certainly will pave the way for osmotic delivery systems to play an increasingly important role in drug delivery.

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